The small intestine is an important source of adrenomedullin release during polymicrobial sepsis

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Zhou, Mian, Irshad H. Chaudry, and Ping Wang. The small intestine is an important source of adrenomedullin release during polymicrobial sepsis. Am J Physiol Regulatory Integrative Comp Physiol 281: R654–R660, 2001.—Adrenomedullin (AM), a potent vasodilatory peptide, has recently been reported to be involved in the altered cardiovascular responses under various pathophysiological conditions. Although the increase in plasma AM levels is associated with upregulation of AM gene expression in various tissues, it remains unknown whether the gut is an important source of AM release under such conditions. To determine this, adult male rats were subjected to sepsis by cecal ligation and puncture (CLP) followed by fluid resuscitation. Systemic and portal blood samples were collected simultaneously at 10 and 20 h after CLP or sham operation. A portion of the jejunum was also harvested. Plasma and tissue levels of AM were then determined by RIA. The localization of AM in the intestinal tissue was examined using immunohistochemistry. In an additional group of normal rats, synthetic rat AM (8.5 μg/kg body wt) was infused for 15 min at a constant rate via the portal vein (which produces a similar level of AM as observed during sepsis). Cardiac output, stroke volume, total peripheral resistance, and microvascular blood flow in various organs were determined before and 30 min after AM administration. The results indicate that AM levels in portal blood were significantly higher than in systemic blood at 10 and 20 h after CLP. Intestinal AM was also markedly elevated. Immunohistochemical visualization shows that AM immunostainings were localized in the mucosa, submucosa, and intestinal nerve fibers, and they were increased at 10–20 h post-CLP. Because AM-immunopositive nerve fibers increased in the gut during sepsis, a nerve pathway may be involved in the regulation of vascular reactivity by this peptide. Moreover, intraportal administration of AM increased cardiac output, stroke volume, and microvascular blood flow in the liver, kidney, small intestine, and spleen. In contrast, total peripheral resistance was significantly reduced. Thus the gut plays an important role in increasing the levels of circulating AM during the progression of sepsis. Gut-derived AM appears to be a major factor in initiating the hyperdynamic response after the onset of sepsis.

Despite advances in the management of the septic patient as well as the understanding of pathophysiological mechanisms of sepsis, the high mortality rate due to sepsis, septic shock, and the ensuing multiple organ failure has not been significantly reduced in the past two decades (1, 2). In the model of sepsis by cecal ligation and puncture (CLP), the cardiovascular response is characterized by hyperdynamic circulation at the early stage and hypodynamic circulation at the late stage of sepsis (32, 36, 38). However, the mediators or factors responsible for producing the transition from the early hyperdynamic to the late hypodynamic phase of sepsis have not been fully understood. Adrenomedullin (AM) is a potent vasodilatory peptide and is expressed in a variety of tissues or cell populations such as cultured endothelial cells and vascular smooth muscle cells, the heart, lungs, kidneys, and intestines (3, 10, 25, 27). Clinical reports have indicated that circulating levels of AM increased significantly in patients with septic shock (7, 19), and a good correlation was observed between the plasma concentrations of AM and various hemodynamic parameters (18). The elevated plasma levels of AM during sepsis appear to be associated with the hyperdynamic state, characterized by high cardiac output (CO) and systemic vasodilation (18). Although our previous studies have indicated that plasma AM is increased during sepsis (35), the sources of AM production and release under such conditions remain unknown. In this regard, studies have suggested that the highest increase in AM mRNA after endotoxin administration occurs in the gut compared with other organs (23, 24). However, it remains unknown whether the small intestine is indeed an important source of AM production and release during sepsis. Therefore, the aim of this study was to determine the role of the gut in producing and releasing AM during the progression of sepsis by examining AM levels in systemic and portal blood as well as in intestinal tissue. The immunolocalization of AM in the gut was also examined. In addition, the effect of intraportal administration of AM on various hemodynamic parameters was also determined in nonseptic animals.

Materials and methods

Animal model of sepsis. Polymicrobial sepsis was induced in male Sprague-Dawley rats (275–325 g, Charles River...
Laboratory, Wilmington, MA) by CLP as described previously (4). Briefly, rats were fasted overnight before the induction of sepsis but were allowed water ad libitum. The animals were anesthetized with methoxyflurane inhalation, and a 2-cm ventral midline incision was made. The cecum was then exposed, ligated just distally to the ileocecal valve to avoid intestinal obstruction, punctured twice with an 18-gauge needle, and returned to the abdominal cavity. The abdominal incision was then closed in layers, and the animals received 3 ml/100 g body wt normal saline subcutaneously immediately after CLP to provide fluid resuscitation. Sham-operated animals underwent the same surgical procedure except that the cecum was neither ligated nor punctured. The animals were then divided into four groups. Two groups of CLP animals and two groups of sham-operated animals were studied at 10 and 20 h after CLP or sham operation. It should be noted that 10 h after CLP represents the early hyperdynamic stage of sepsis and 20 h after CLP represents the late hypodynamic stage of sepsis (32). The experiments described here were performed in adherence to the Institutional Guidelines of the University of Alabama at Birmingham. The protocol was approved by the Institutional Animal Care and Use Committee of the University of Alabama at Birmingham.

Plasma AM determination. At 10 or 20 h after CLP or sham operation (6–8 rats/group), portal and systemic blood samples were collected simultaneously into heparinized syringes via the portal vein and by cardiac puncture, respectively, and then transferred to polypropylene tubes containing EDTA (1 mg/ml) and aprotinin (500 KIU/ml). The plasma was immediately separated and stored at −70°C until assayed. Plasma levels of AM were quantified by using RIA kits specific for rat AM according to the procedure provided by the manufacturer (Peninsula Laboratories, Belmont, CA). Briefly, AM was extracted from 0.5 ml plasma on C18 manufacturer (Peninsula Laboratories, Belmont, CA). Plasma levels of AM were determined by using EDTA (1 mg/ml) and aprotinin (500 KIU/ml). The plasma rings via the portal vein and by cardiac puncture, respectively immediately after the death of the animals by an overdose of pentobarbital sodium.

Tissue AM determination. A portion of jejunum was harvested immediately after the death of the animals by an overdose of pentobarbital sodium at 10 or 20 h after CLP or sham operation (6–8 rats/group). The tissue (0.5 g) was homogenized with 2 ml Tris-HCl (50 mM, pH 7.4) and centrifuged at 16,000 g for 10 min. The supernatant was collected and stored at −70°C until assayed. Tissue levels of AM were measured by using an RIA kit specific for rat AM from Peninsula Laboratories as described above. Tissue levels of AM were expressed as picograms per milligram of protein, and protein concentration in the supernatant was determined by the Lowry method (16).

AM immunohistochemistry. Similar portions of the small intestine (jejunum) were collected immediately after the death of the animals by an overdose of pentobarbital sodium at 10 and 20 h after CLP or sham operation in additional groups of animals (3 rats/group). The tissue was fixed overnight in 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4) and washed with 0.1 M phosphate buffer (pH 7.4). The tissue was then cut into 30-μm sections using a vibratome. Preembedding immunohistochemistry was performed as previously described by us (42). Briefly, the tissues were incubated with Tris-buffered saline (TBS) containing 0.1% Triton X-100, 3% normal goat serum, and 1% dry milk for 1 h. The tissues were then incubated with the specific rabbit polyclonal antibody against rat AM (Peninsula Laboratory) at a dilution of 1:1,000 for 60 h at 4°C. After the sections were rinsed with TBS, they were incubated in 3% H2O2 containing 70% methanol for 30 min. The tissues were then transferred to a biotinylated goat anti-rabbit IgG antiserum (Vector Laboratories, Burlingame, CA) for 30 min at room temperature and followed by a reaction with an avidin-biotin-peroxidase complex (Vector Laboratories) for 1.5 h at room temperature. The reaction products were revealed by placing the tissues into 3,3′-diaminobenzidine (Sigma Chemical, St. Louis, MO) solution. The sections were mounted on slides for light-microscopy evaluation, which was judged blindly. For negative control, nonimmunized rabbit serum was substituted for the primary antibody.

Intraportal infusion of synthetic rat AM. Male Sprague-Dawley rats (275–325 g) were fasted 16 h before the experiment but were allowed water ad libitum. The animals were anesthetized with methoxyflurane inhalation, and the left femoral artery was cannulated with PE-50 tubing for monitoring blood pressure and heart rate. After a midline incision, a branch of the superior mesenteric vein was isolated and cannulated with PE-10 tubing for AM administration. The tip of the catheter was advanced to the level of the portal vein. This procedure did not cause any apparent ischemia. Subsequent anesthesia was maintained by intravenous injection of pentobarbital sodium (~30 mg/kg body wt). After 30–60 min of stabilization, synthetic rat AM at a dose of 8.5 μg/kg body wt in normal saline solution containing 8.5 μg/kg AM and 0.2% bovine serum albumin or an equivalent volume of vehicle (i.e., normal saline with 0.2% bovine serum albumin) was infused via the portal catheter over 15 min at a constant infusion rate (n = 6/group). The synthetic rat AM 1–50 used in this study was purchased from Peninsula Laboratories. Determination of various hemodynamic parameters was performed before as well as at 30 min after the completion of AM or vehicle infusion. The animals were then killed at the end of the experiment by an overdose of pentobarbital sodium.

Determination of CO and microvascular blood flow. Measurement of CO was performed using an indocyanine green dilution technique with a 2.4 French fiberoptic catheter and in vivo hemorectector, as described previously by us (28). CO was calculated according to the principle of dye dilution. Stroke volume (SV) and total peripheral resistance (TPR) were then calculated. Microvascular blood flow on the surface of the liver, small intestine, kidney, and spleen was determined by laser-Doppler flowmetry (Laserflo, model BPM 403A, TSI, St. Paul, MN) (28). The measured flow was the microvascular red blood cell flux in ~1 mm2 on the surface of each organ with a unit of milliliters per minute per 100 g tissue, as indicated by the manufacturer. Although this is a reliable technique for determining the alterations in organ surface perfusion, the flow unit suggested by the manufacturer should be considered as arbitrary rather than absolute units.

Statistical analysis. All data are expressed as means ± SE. One-way ANOVA and Tukey’s test or Student’s t-test were used, and differences in values were considered significant if P ≤ 0.05.

RESULTS

Portal and systemic levels of AM. As shown in Fig. 1, systemic and portal levels of AM increased signifi-
cantly at 10 and 20 h after CLP compared with sham-operated animals. Although the levels of AM were similar in portal and systemic samples in sham-operated animals, AM levels in portal blood increased significantly compared with systemic blood at 10 h after CLP ($P < 0.05$; Fig. 1). Similar results were also observed at 20 h after the onset of sepsis.

**AM levels in the small intestine.** Intestinal levels of AM were $7.5 \pm 0.5$ and $8.0 \pm 0.8$ pg/mg protein at 10 and 20 h after sham operation, respectively (Fig. 2). At 10 and 20 h after CLP, however, tissue AM levels increased by 179% and 72%, respectively ($P < 0.05$; Fig. 2).

**AM immunohistochemistry.** In sham-operated animals, there were no apparent immunostainings in intestinal glands and smooth muscle, but epithelial cells of villi were slightly stained (Fig. 3A). In contrast to the weak AM immunostainings at 20 h after sham operation (Fig. 3A), the immunostainings increased markedly at 10 (Fig. 3B) and 20 h (Fig. 3C) after the onset of sepsis. AM immunostainings were primarily located in connective tissues of the mucosa and submucosa as well as in intestinal nerve fibers that surrounded intestinal glands and small blood vessels (Fig. 3, B and C). In the negative control section (i.e., substitution of the primary antibody with a nonimmunized rabbit serum), AM immunoreaction was not observed (Fig. 3D).

**Effects of intraportal administration of AM on various hemodynamic parameters.** As shown in Table 1, administration of AM at a dose of 8.5 $\mu$g/kg in normal animals increased CO and SV by 39.5% and 42.6% ($P < 0.05$), respectively, at 30 min after the infusion. In contrast, TPR decreased by 34.9% ($P < 0.05$) at the same time point. Similar to CO and SV, microvascular blood flow in the liver, kidney, small intestine, and spleen increased by 35.9–74.5% ($P < 0.05$) at 30 min after the completion of AM infusion (Table 2).

**DISCUSSION**

AM is a potent vasodilatory peptide with 52 amino acid residues in the human and 50 amino acid residues in the rat (11, 22). It plays an important role in regulating the cardiovascular response under various pathophysiological conditions. Studies have indicated that the increased levels of circulating AM were associated with heart failure and renal failure, particularly during sepsis, in which the highest levels of circulating AM were observed (7–9, 12). In this regard, we have recently reported that plasma levels of AM were significantly elevated during the early and late stages of polymicrobial sepsis (35). In addition, systemic infusion of synthetic rat AM at a dose of 8.5 $\mu$g/kg increased CO, SV, and microvascular blood flow in various organs and decreased TPR (31). Moreover, administration of anti-AM antibodies prevented the occurrence of the hyperdynamic response observed during the early stage of sepsis (31). These findings, taken together, suggest that AM plays an important role in producing the hyperdynamic circulation after the onset of sepsis. Although it has been reported that AM mRNA is expressed in a variety of tissues and cell populations (3, 22), the primary source of AM release during sepsis remains unknown. Because AM gene expression is upregulated in the small intestine during sepsis (35) and because our previous studies have demonstrated that the increased portal blood flow is responsible for the increased hepatic perfusion during the early stage of sepsis (29), we hypothesized that the gut is an important source of AM production and release during sepsis.

Our results show that AM levels in portal blood were significantly higher than those in the systemic blood at 10 and 20 h after CLP. The increase in portal AM levels was associated with an elevation in intestinal AM levels. In addition, AM immunohistochemical stainings in the gut were increased at 10 and 20 h after CLP. Thus the intestine plays a role in increasing the levels of circulating AM during the early and late stages of sepsis. Moreover, intraportal administration
of AM increased CO, SV, and microvascular blood flow in the liver, kidney, small intestine, and spleen. In contrast, TPR was significantly reduced. Thus gut-derived AM appears to be an important factor in initiating the hyperdynamic response after the onset of polymicrobial sepsis. The dose of AM for the intraportal administration was 8.5 \( \mu g/kg \) for a period of 15 min at a constant infusion rate. This was chosen because our previous study has indicated that systemic administration of synthetic rat AM at a dose of 8.5 \( \mu g/kg \) (same as used in the present study) produces a hyperdynamic response without significantly affecting blood pressure and heart rate (31). In addition, plasma levels of AM were found to be 691.1 \( \pm 28.2 \) pg/ml at 30 min after AM administration (31), a level similar to that in septic animals in the present study (Fig. 1). Although plasma levels of AM in the portal and systemic blood

Table 1. Alterations in CO, SV, and TPR before and 30 min after intraportal administration of AM

<table>
<thead>
<tr>
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<th>Before</th>
<th>30 min After</th>
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<tbody>
<tr>
<td>CO, ml·min(^{-1})·100 g(^{-1})</td>
<td>29.9 (\pm) 3.0</td>
<td>41.7 (\pm) 5.2(^*)</td>
</tr>
<tr>
<td>SV, (\mu l)·beat(^{-1})·100 g(^{-1})</td>
<td>98.9 (\pm) 7.5</td>
<td>141.0 (\pm) 19.9(^*)</td>
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<tr>
<td>TPR, mmHg·ml(^{-1})·min(^{-1})·100 g(^{-1})</td>
<td>4.27 (\pm) 0.42</td>
<td>2.78 (\pm) 0.44(^*)</td>
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Values are means \(\pm\) SE \((n = 6)\) and compared by paired Student’s \(t\)-test: \(^*P < 0.05\) after vs. before. CO, cardiac output; SV, stroke volume; TPR, total peripheral resistance; AM, adrenomedullin.

Table 2. Alterations in microvascular blood flow (arbitrary units) before and 30 min after intraportal administration of AM

<table>
<thead>
<tr>
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<th>Before</th>
<th>30 min After</th>
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<tr>
<td>Liver</td>
<td>37.9 (\pm) 1.2</td>
<td>59.3 (\pm) 7.4(^*)</td>
</tr>
<tr>
<td>Kidney</td>
<td>71.5 (\pm) 3.6</td>
<td>102.2 (\pm) 6.1(^*)</td>
</tr>
<tr>
<td>Small intestine</td>
<td>87.1 (\pm) 3.5</td>
<td>118.4 (\pm) 8.0(^*)</td>
</tr>
<tr>
<td>Spleen</td>
<td>20.8 (\pm) 0.8</td>
<td>36.3 (\pm) 1.6(^*)</td>
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Values are means \(\pm\) SE \((n = 6)\) and compared by paired Student’s \(t\)-test: \(^*P < 0.05\) after vs. before.
were not determined in this study, it is logical to assume that portal levels of AM would be higher than the systemic level during the infusion of AM and the levels of AM in portal and systemic blood would be similar at 30 min after the completion of AM infusion. It should be noted that the liver does not appear to be the site for AM clearance, because the lungs are responsible for reducing circulating levels of AM in sepsis (20).

Because the lungs rather than the liver are the major sites for AM clearance (20), we would expect that administration of AM via the portal vein is effective in producing the hyperdynamic response as administration via a systemic route. However, due to the fact that the gut is a major source of AM production and that the gut plays an important role in initiating the hyperdynamic response during the early stage of sepsis (39), it would be more pathophysiologically relevant to infuse synthetic AM via the portal vein than via a systemic catheter. Our present data further confirm our previous findings that the elevated plasma AM plays an important role in initiating the hyperdynamic response. Furthermore, the gut-derived AM is critical in the elevation of systemic levels of AM and the initiation of the hyperdynamic response during the early stage of sepsis.

It should be noted that studies have been conducted to further examine the role of AM in initiating the hyperdynamic response during the early stage of sepsis. In our recent publication (31), specific anti-rat AM antibodies were administered at 1.5 h after CLP, and various hemodynamic variables were measured 5 h after the onset of sepsis. The results indicated that CO, SV, and microvascular blood flow in various organs increased and TPR decreased at 5 h after CLP. Administration of anti-AM antibodies, however, prevented the occurrence of the hyperdynamic response under such conditions (31). These results clearly indicate that the elevated levels of AM indeed play an important role in producing the hyperdynamic response observed during early sepsis. Although we have previously shown that systemic levels of AM increase in sepsis (35), it remains unknown whether the gut is the major source of AM production under such conditions. The novel findings of the current study are that the gut plays an important role in increasing the circulating levels of AM in sepsis. Furthermore, intraportal infusion of synthetic AM produces the hyperdynamic response similar to that observed during the early stage of sepsis, indicating the pathophysiological significance of gut-derived AM. This is an important finding because we have previously shown that the increase in total hepatic blood flow during early sepsis is mainly due to the increased portal blood flow (29). Thus the present study does provide new information for our understanding of the role of AM in sepsis.

It has been demonstrated that the cardiovascular response is characterized by hyperdynamic circulation at the early stage and hypodynamic circulation at the late stage of sepsis in the CLP model of sepsis in the rat and mouse (32, 36–38). The hyperdynamic response occurs at 2–10 h after CLP, and the hypodynamic response occurs at 16 h or later after the onset of sepsis (32, 33). In a typical time point of the hyperdynamic response (i.e., 5 h after CLP), CO and SV increase by 34 and 29%, respectively, and TPR decreases by 19% (38). In contrast, CO and SV decrease by 41 and 50%, and TPR increases by 70% at 20 h after CLP (a typical time point of the hypodynamic response) (38). Regarding the transition from the hyperdynamic to hypodynamic response during the progression of sepsis, our recent data have shown that this appears to be due to the reduction in vascular responsiveness to AM (13, 34). In this regard, we reported that AM-induced vascular relaxation decreased significantly at 20 h after CLP in aortic rings and resistance blood vessel in the gut (34). Thus we propose that AM hypo responsiveness is responsible for the transition from the early hyperdynamic to late hypodynamic response in sepsis (14).

It should be noted that the limitation of immunohistochemistry and RIA is that it is difficult to differentiate gut-synthesized AM and the AM deposited in the intestinal tissue via circulation despite the fact that the anti-rat AM antibodies used in this study are specific. Because PCR in situ hybridization was not performed in the gut, the precise location or cell population responsible for AM synthesis remains unknown. However, the fact that intestinal AM gene expression increased by 422–553% at 10–20 h after CLP, as shown in our previous publication (35), suggests that the gut is indeed an important organ in producing AM during sepsis. In the present study, portal levels of AM were found to be 42% and 37% higher than systemic levels at 10 and 20 h after CLP, respectively. In addition, intestinal levels of AM increased by 179% and 72% at those time points. These results, taken together, strongly suggest that the gut plays an important role in the synthesis and release of AM during sepsis. Although the immunohistochemical staining shows increased AM levels in the gut at both 10 and 20 h after the onset of sepsis, intestinal levels of this peptide at 20 h after CLP (as determined by RIA) decreased by 36% compared with those at 10 h after CLP (Fig. 2). This could be the result of the loss of intestinal proteins due to edema and cellular damage at 20 h after the onset of sepsis. Moreover, it has been demonstrated that specific AM binding proteins (i.e., AMBP-1) exist in plasma (5, 21). Although we have not determined changes in AMBP-1 in sepsis, Elsasser et al. (5) reported that AM binding proteins decreased significantly in the plasma of calves undergoing an acute phase response to a parasitic infection. The reduced plasma levels of AMBP-1 during infection could be due to the increase in the deposition of this binding protein in tissues such as the gut. Because the conventional RIA for AM is limited to only assay the non-bound portion of the AM pool (21), it is possible that the postulated increase in intestinal AMBP-1 is responsible for the reduced tissue levels of AM at 20 h after CLP.

Although Cameron and Fleming (3) reported that AM gene expression increased in the mucosa and sub-
mucosa of the small intestine by an in situ hybridization technique, the precise immunohistochemical localization of this peptide in the small intestine was not examined in that study. The results of the present study indicate that AM-positive immunostainings were localized at the mucosa and submucosa of the small intestine during sepsis, which was similar to the distribution of AM mRNA (3). AM immunoreaction products were primarily located in connective tissues of the lamina propria and submucosa. In addition, AM immunoreaction products were also observed in the intestinal nerve fibers that surround the intestinal glands and small blood vessels. To the best of our knowledge, this is the first report indicating that AM-positive immunostainings are localized in the intestinal nerve fibers during polymicrobial sepsis. Thus connective tissues of the lamina propria and submucosa and intestinal nerve fibers are responsible for AM production in the small intestine during sepsis. Although the precise mechanism responsible for upregulation of AM production in the gut remains unknown, studies have shown that endotoxin and proinflammatory cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β increase AM production in cultured cells (26). In addition, circulating levels of TNF-α, IL-1β, and IL-6 have been reported to be elevated during sepsis (6, 15), and the increased levels were associated with upregulation of their mRNAs in Kupffer cells very early after the onset of sepsis (17, 30). These findings, taken together, would suggest that the increased endotoxin (6) and proinflammatory cytokines during polymicrobial sepsis may play an important role in upregulating AM production in the small intestine.

In summary, our results indicate that AM levels in portal blood were significantly higher than those in systemic blood during the early and late stages of sepsis. Similarly, AM levels in the intestinal tissue were also elevated. Moreover, AM immunohistochemistry shows that AM immunostainings were increased at 10 and 20 h after CLP. Thus the gut appears to be an important source of AM production and release after the onset of sepsis. In addition, gut-derived AM appears to be a major factor in initiating the hyperdynamic response after the onset of sepsis. Because AM-positive nerve fibers are observed in the small intestine, which are more prominent during sepsis, an intestinal nerve pathway may be involved in the regulation of vascular reactivity by this peptide.

Perspectives

Septic shock and multiple organ failure continue to be the major causes of mortality in intensive care units. The typical cardiovascular response to polymicrobial sepsis is characterized by an early hyperdynamic phase followed by a late hypodynamic phase. Although the factors and/or mediators responsible for producing the transition from the hyperdynamic to the hypodynamic stage are not fully understood, recent studies have suggested that AM, a potent vasodilatory peptide, appears to play an important role in initiating the hyperdynamic response during the early stage of sepsis. In addition, the reduced vascular responsiveness to AM may result in the transition from the early hyperdynamic phase to the late hypodynamic phase of sepsis. Despite the fact that AM gene expression is upregulated in various tissue and plasma levels of this peptide are increased in sepsis, the primary source of AM production remains unknown. This study has clearly demonstrated that the gut appears to be the major organ responsible for the increase in AM in sepsis. Although gut-derived AM plays an important role in initiating the hyperdynamic response after the onset of sepsis, AM may also have direct effects on intestinal vasculature. This hypothesis is supported by the findings that prior enterectomy prevented the occurrence of the hyperdynamic response during the early stage of sepsis (39). In addition, this study also points out the possibility that intestinal nerve pathways may be involved in the regulation of vascular reactivity by AM. Future studies are required to determine the mechanisms responsible for the increased AM production in the gut and its interaction with other gut-derived mediators such as calcitonin gene-related peptide (41) and norepinephrine (40) during sepsis.

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GUT-DERIVED ADRENOMEDULLIN IN SEPSIS


